

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 June 2001 (21.06.2001)

PCT

(10) International Publication Number
WO 01/44449 A1

(51) International Patent Classification⁷: C12N 9/16, (74) Agent: GIDDINGS, Barton; Madson & Metcalf, Suite 900, 15 West South Temple, Salt Lake City, UT 84101 (US).

(21) International Application Number: PCT/US00/34045

(22) International Filing Date:
14 December 2000 (14.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/170,562 14 December 1999 (14.12.1999) US

(71) Applicant (for all designated States except US): UNIVERSITY OF UTAH RESEARCH FOUNDATION [US/US]; Suite 110, 615 Arapeen Drive, Salt Lake City, UT 84108 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): BOLGER, Graeme [CA/US]; University of Alabama, Comprehensive Cancer Center, WTI 520, 1530 3rd Avenue South, Birmingham, AL 35294-3300 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/44449 A1

(54) Title: TWO NOVEL cAMP-SPECIFIC PHOSPHODIESTERASE (PDE4B) ISOFORMS AND RELATED TECHNOLOGY

(57) Abstract: Two novel cAMP-specific isoforms of rat PDE4B are disclosed. pRPDE90 is a cDNA encoding a 659-amino acid-long protein with a large region corresponding to similar regions found in PDE4B1 and PDE4B3. It is separated from these isoforms by a 17-amino acid region found at its extreme amino-terminal end which shows no homology to any previously-cloned sequence. pRPDE89 is a rat cDNA which encodes a 726-amino acid-long protein which is 96 % identical to the human PDE4B1 phosphodiesterase isoform.

TWO NOVEL cAMP-SPECIFIC PHOSPHODIESTERASE (PDE4B) ISOFORMS AND RELATED TECHNOLOGY

1. Related Applications

5 This application is related to and claims the benefit of United States Provisional Application Serial No. 60/170,562 of Graeme B. Bolger, filed December 14, 1999 and entitled "Two Novel cAMP-Specific Phosphodiesterase (PDE4B) Isoforms and Related Technology," which is incorporated herein by reference.

10 2. Field of the Invention

The present invention relates to cyclic AMP-specific phosphodiesterases (PDE4 enzymes), which help regulate physiological processes by hydrolyzing cAMP, an intracellular signaling molecule. Specifically, the invention relates to two novel cAMP-specific phosphodiesterase isoforms which are expressed in many body tissues, including
15 the brain.

3. Technical Background

Cyclic AMP ("cAMP") is an intracellular signaling molecule involved in many important cellular processes. Specifically, cAMP is critical to signaling pathways which regulate physiological processes such as those involved in vascular smooth muscle, the immune system, and the brain. cAMP-specific phosphodiesterases, referred to as "PDE4 enzymes," hydrolyze cAMP and thus regulate these pathways in cells. The cAMP-specific phosphodiesterases can be differentiated from other cyclic nucleotide phosphodiesterase ("PDE") families by sequence homology in the catalytic region of the proteins as well as by their ability to be inhibited by a specific class of drugs, such as rolipram. Beavo, *Physiol. Rev.* 75:725–48 (1995). Rolipram and other specific PDE4 inhibitors have anti-depressant, anti-inflammatory and smooth muscle relaxant properties in humans. Houslay et al., *Advances in Pharmacology*, 44:225–342 (1998). PDE4 enzymes are also characterized by the presence of unique "signature" regions of sequence, called upstream conserved regions, or "UCR," such as UCR1 and UCR2, which are located in the amino-terminal third of the proteins. Houslay, et al., *supra*; Bolger et al., *Mol. Cell Biol.*, 13:6558–71 (1993).

PDE4 enzymes are also the closest vertebrate homologs of the *dunce* gene of *Drosophila melanogaster*, which was isolated as a mutation affecting learning and memory. Davis, *Physiol. Rev.* 76:299–317 (1996). The mammalian PDE4s are encoded by four genes (*PDE4A*, *PDE4B*, *PDE4C* and *PDE4D*), and it has been shown by several researchers that additional diversity in this family is produced by alternative mRNA splicing. Bolger et al., *supra*; Sette et al., *J. Biol. Chem.*, 269(32):20806 (Aug. 12, 1994); Bolger et al., *J. Biol. Chem.*, 271:1065–71 (1996); Bolger et al., *Biochem. J.*, 328:539–48 (1997); Naro et al., *Endocrinology*, 137:2464–72 (1996); Huston et al., *Biochem J.* 328:549–56 (1997). See Houslay et al., *supra*, for a review of these findings. Often the alternatively-spliced isoforms have different tissue expression patterns, a fact which suggests that each may have a distinct function.

Intracellular signaling molecules are important since they transmit a signal received outside of the cell to target molecules in the cytosol, thus allowing a cell to react to changes in its environment. This transmission is generally a multistep process often having at least the general steps laid out in the following cAMP-specific sequence: First, an extracellular ligand binds to a plasma membrane-bound receptor molecule which has a binding domain extending into the extracellular space and a domain extending into the cytosol. Second, the binding of the ligand to the extracellular domain changes the conformation of the cytosolic domain, thus causing it to bind to a G-protein. Third, the G-protein, in turn, activates a plasma membrane enzyme which produces cAMP (adenylyl cyclase). Fourth, the cAMP then binds to target molecules in the cytosol, thus altering their conformation and activity. Finally, cyclic AMP-specific phosphodiesterases rapidly break down the cAMP, hydrolyzing it to form adenosine 5'-monophosphate.

As seen in the final step, in order to use cAMP as a signaling molecule, a cell must be able to quickly manipulate the levels of cAMP present in response to signals transmitted to the outside of the cell. Cyclic AMP functions well in this respect, having been shown in some cases to respond to hormonal stimulation by increasing in cellular concentration by five-fold within seconds.

Such rapid changes in cAMP levels are possible due to a cell's ability to rapidly synthesize cAMP. Cells are also adapted to rapidly break down cAMP. Cyclic AMP is synthesized from ATP by adenylyl cyclase, an enzyme found in the plasma membrane of a cell. Cyclic AMP is hydrolyzed by cyclic AMP phosphodiesterases to form adenosine

5'-monophosphate ("5'-AMP"). These phosphodiesterases are found in many tissues, including specific regions of the brain.

It is known that certain cAMP-specific phosphodiesterases ("PDE4 enzymes") are the targets of inhibitors. Some of these inhibitors have been shown to have positive effects on the brain, including exhibiting anti-depressant properties, memory-enhancing qualities, and other positive effects on the function of the central nervous system. Unfortunately, however, these beneficial effects are often accompanied by nausea and other gastrointestinal side effects. These negative side effects are likely mediated at least in part by the action of the inhibitors used on the brain. The number of isoforms of the PDE4 enzymes present in the brain is currently unknown, as is an understanding of which inhibitors affect which phosphodiesterases. Knowledge of novel isoforms of PDE4 enzymes would be a great advancement in the art, allowing researchers and health professionals to learn to target PDE4 inhibitors to specific isoforms and limit the effects of the inhibition to the desired, positive effects, while avoiding inhibition of those isoforms whose inhibition causes the deleterious side effects noted above.

From the foregoing, it will be appreciated that it would be an advancement in the art to identify additional PDE4 enzyme isoforms. Such identification would enable investigation of the patterns of isoform tissue expression, and thus allow selective targeting of specific isoforms with isoform-specific inhibitors, yielding effective use of the beneficial effects of inhibition while avoiding the deleterious ones.

Such novel PDE4 enzyme isoforms are disclosed herein.

4. Brief Summary of the Invention:

The present invention relates to isoforms of cAMP-specific phosphodiesterase. Specifically, two rat cDNAs, pRPDE89 and pRPDE90, were isolated from a rat cerebral cortex cDNA library. Both of these were found to encode novel PDE4B isoforms. The invention thus comprises a first cDNA, pRPDE89, which encodes a protein identical in length to that encoded by the previously-described human PDE4B1 isoform known in the art. The protein encoded by both the rat and human genetic material is 736 amino acids in length. This rat cAMP-specific phosphodiesterase isoform is over 96% identical in sequence to the human PDE4B1 isoform.

The invention further comprises a second cDNA, pRPDE90, which encodes a

novel protein of 659 amino acids, called PDE4B4. PDE4B4 has a novel N-terminal region of 17 amino acids which is not present in any other known PDE4B isoform. The remaining 642 amino acids of PDE4B4 are identical to those found in corresponding regions of the PDE4B1 and PDE4B3 isoforms. Without being bound to any particular theory, it is believed that the structures of the cDNAs encoding the PDE4B1, PDE4B3, and PDE4B4 isoforms are generated by alternative mRNA splicing and through the use of alternative promoters of the *PDE4B* gene. RNase protection and immunoblotting demonstrated the presence of mRNA and protein specific for each of the PDE4B1, PDE4B2, PDE4B3 and PDE4B4 isoforms, respectively, in a wide range of tissues, including various regions of the brain.

Since various inhibitors of cAMP phosphodiesterases have been shown to have anti-depressant and memory enhancement effects, the discovery of novel isoforms of PDE4B opens possibilities of better understanding and targeting such inhibitors to have more selective effects on the brain.

These and other features of the present invention will become apparent upon reference to the accompanying figures and upon reading the following detailed description and appended claims.

5. Brief Description of the Drawings

A more particular description of the invention briefly described above will be rendered by reference to the appended figures. These figures only provide information concerning typical embodiments of the invention and are not therefore to be considered limiting of its scope.

Figure 1 shows the structure of mRNAs encoded by the rat *PDE4B* gene. The numbers 1-4 indicate transcripts represented by the following cDNAs: 1, PDE4B1 (pRPDE89 (SEQ ID NO: 5); GenBank™ AF202732); 2, PDE4B2 (pRPDE18 (SEQ ID NO: 8); GenBank™ L27058); 3, PDE4B3 (pRPDE74 (SEQ ID NO: 9); GenBank™ U95748); 4, PDE4B4 (pRPDE90 (SEQ ID NO: 1) and pRPDE92 (SEQ ID NO: 10); GenBank™ AF202733). The heavy bar indicates sequences homologous to other PDE4 isoforms, with the strongest regions of conservation (the catalytic region and UCR1 and UCR2) indicated by the cross-hatched areas. The thin, branched lines adjacent to the numbers indicate sequence regions unique to each isoform. The thin lines merge where

the sequences of the various isoforms join the shared sequence. Small boxes indicate start codons and the asterisk indicates the common stop codon.

Figure 2 shows an alignment of the amino acid sequences of human PDE4B1 (top, SEQ ID NO: 7) and rat PDE4B1 (bottom, SEQ ID NO: 6). The sequence of human PDE4B1 has been described previously (pTM72 in Bolger, *Mol. Cell Biol.* 13:6558-71 (1993), GenBank™ L20966). The sequence of PDE4B1 was deduced from the pRPDE89 cDNA.

Figure 3 shows an alignment of the amino acid sequences of rat PDE4B1 (SEQ ID NO: 6), PDE4B2 (SEQ ID NO: 8), PDE4B3 (SEQ ID NO: 9), and PDE4B4 (SEQ ID NO: 2). The sequences are derived from the following cDNAs: PDE4B1 (pRPDE89 (SEQ ID NO: 5); GenBank™ AF202732); PDE4B2 (pRPDE18 (SEQ ID NO: 10); GenBank™ L27058); PDE4B3 (pRPDE74 (SEQ ID NO: 11); GenBank™ U95748); PDE4B4 (pRPDE90 and pRPDE92; GenBank™ AF202733).

Figure 4 shows the nucleotide sequence (SEQ ID NO: 1) encoding PDE4B4. The sequences of two plasmids, pRPDE90 and pRPDE92, have been merged. On the merged sequence, pRPDE92 corresponds to nucleotides 1 to 1936, and pRPDE90 corresponds to nucleotides 253 to 2433. This sequence is available as GenBank™ AF202733.

Figure 5 shows the nucleotide sequence of pRPDE89 (SEQ ID NO: 5), which encodes PDE4B1. This sequence is available as GenBank™ AF202732.

6. Detailed Description of the Invention

The present invention provides two novel cAMP-specific phosphodiesterase (PDE4B) isoform cDNAs. These cDNAs encode phosphodiesterases, which function in the regulation of physiological processes by hydrolyzing cAMP, an intracellular signaling molecule derived from ATP.

The first cAMP-specific phosphodiesterase isoform cDNA is pRPDE90, a phosphodiesterase isolated from a rat (*Rattus norvegicus*; Sprague-Dawley strain) cerebral cortex cDNA library cloned into the Eco RI site of Lambda ZAPII, which was obtained from Stratagene. This cDNA encodes a novel PDE4B isoform named PDE4B4 by the inventors in accordance with convention.

PDE4B4 is a novel PDE4B isoform comprising 659 amino acids, 642 of which are shared with the other "long" isoforms of PDE4B: PDE4B1 and PDE4B2. The remaining 17 amino acids are found at the extreme amino-terminal end of the protein.

The second cAMP-specific phosphodiesterase isoform cDNA of the instant invention is pRPDE89, a novel rat cDNA. pRPDE89 encodes a protein comprising 736 amino acids. This protein is identical in length and 96% identical in amino acids to the human PDE4B1 isoform (712 of 736 amino acids are identical). Without being bound to any particular theory, it appears that pRPDE89 encodes the rat counterpart of the human PDE4B1 isoform of PDE4B.

The present invention provides isolated and purified nucleic acid molecules comprising nucleotides that encode the amino acid sequences of SEQ ID NOS: 2, 4, and 6. In certain embodiments, these nucleic acid molecules comprise nucleotides 262 to 2238 of SEQ ID NO: 1, nucleotides 1 to 51 of SEQ ID NO: 3, and nucleotides 325 to 2532 of SEQ ID NO: 5, respectively. The present invention also provides nucleic acid molecules that encode amino acid sequences that are greater than 90%, greater than 85%, greater than 80%, greater than 75%, and greater than 70% identical to SEQ ID NO: 4. The present invention also provides such nucleic acid molecules subcloned into plasmids; such nucleic acid molecules subcloned into prokaryotic or eukaryotic expression vectors; and such nucleic acid molecules stably or transiently incorporated into a prokaryotic or eukaryotic host cell.

The present invention also provides isolated and purified proteins comprising the amino acid sequences of SEQ ID NOS: 2 and 6 and peptides comprising the amino acid sequence of SEQ ID NO: 4. The present invention further provides antibodies that specifically recognize peptides comprising the amino acid sequence of SEQ ID NO: 4. Such antibodies may be polyclonal or monoclonal antibodies that are prepared according to methods that are well-known in the art. *See, e.g., Harlow & Lane, Antibodies: A Laboratory Manual* (1988).

Novel PDE4B isoforms such as those of the instant invention are of importance for several reasons. One reason is that the isoforms of the present invention are expressed in brain—an important potential target of PDE4 inhibitors. Indeed, cDNAs encoding numerous PDE4 isoforms have previously been isolated from brain. *See e.g., Bolger et al., Mol. Cell Biol.* 13:6558–71 (1993), Huston et al., *Biochem J.* 328:549–56 (1997),

McLaughlin et al., *J.Biol.Chem.* 268:6470–76 (1993), Bolger et al., *Gene*. 149:237–44 (1993), Davis et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:3604–08 (1989), Colicelli et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:3599–3603 (1989), and Engels et al., *FEBS Lett.* 358:305–10 (1995). The brain is thus a target for many of the actions of selective PDE4 inhibitors. It is therefore important to determine exactly which PDE4 isoforms are present in the brain.

PDE4 inhibitors have several demonstrated effects in the human brain, several of which are beneficial, and others of which are harmful. Some of the potential beneficial effects of PDE4 inhibitors include a demonstrated anti-depressant action. Fleischhacker et al., *Neuropsychobiology*, 26:59–64 (1992), Eckmann et al., *Current Therapeutic Research*, 43:291–95 (1988). PDE4 inhibitors may also augment memory and other central nervous system functions. However, PDE4 inhibitors can cause nausea and trigger other gastrointestinal side effects. At least a portion of these deleterious side effects are likely mediated by the action of these drugs in the brain.

Discovery of additional isoforms of the PDE4B phosphodiesterases would open greater possibilities for developing inhibitors that could be specifically targeted at one or more isoforms. Such targeting would allow a more viable approach for utilizing the beneficial properties of these inhibitors in clinical treatment, while selectively avoiding negative side effects.

As a result, a search for novel PDE4 isoforms was initiated in rat brain. Two previously unknown PDE4 isoforms were subsequently isolated. While not being bound to any one particular theory, one of these appears to be the rat homolog of the human PDE4B1 isoform, which has been described previously in the art. Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993). The second novel isoform, called PDE4B4, has a unique 17 amino acid amino-terminal region which is not present in any other PDE4B isoform. It appears likely that PDE4B4 will be similar to other PDE4 isoforms in that it will be highly specific for cAMP and be inhibited by the prototypical PDE4 inhibitor rolipram.

It has previously been shown that the various PDE4 isoforms have different tissue expression patterns. Huston et al., *Biochem J.* 328:549–56 (1997). Indeed, it has even been shown that different isoforms encoded by the same gene may vary substantially in their tissue expression. (Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993), Bolger et al., *J. Biol. Chem.* 271:1065–71 (1996), and Bolger et al., *Gene*. 149:237–44 (1994). Studies are

in progress to determine the pattern of expression of the four known rat PDE4B isoforms, with special emphasis on their expression in various regions of the brain. Such discoveries and studies create the possibility of exploiting differences in the patterns of tissue expression of the various PDE4 isoforms to "target" the effects of PDE4 inhibitors to specific regions of the brain, thus maximizing their positive effects and minimizing or negating their negative effects.

One current explanation for the divergence of the PDE4B1, PDE4B3 and PDE4B4 mRNAs is alternative mRNA splicing. This has been documented as accounting for the existence of the PDE4A and PDE4D isoforms. Bolger et al., *J.Biol.Chem.* 271:1065-71 (1996), Bolger et al., *Biochem J.* 328:539-48 (1997), and Houslay et al., *Advances in Pharmacology* 44:225-342 (1998). Consistent with this explanation, it has been shown that the point of divergence between PDE4B1, PDE4B3 and PDE4B4 corresponds with the major point of alternative mRNA splicing in the *D. melanogaster* *dunce* gene transcripts. It also corresponds with the major point of alternative mRNA splicing in alternatively spliced mRNAs from the human *PDE4A* (Bolger et al., *Mol. Cell Biol.* 13:6558-71 (1993)), *PDE4B* (Huston et al., *Biochem J.* 328:549-56 (1997)) and *PDE4D* (Bolger et al., *Biochem J.* 328:539-48 (1997)) genes. It also corresponds to the 5' end of an exon in the human *PDE4A* (Sullivan et al., *Biochem J.* 333:693-703 (1998)) and murine *Pde4a* (Olsen & Bolger, *Mammalian Genome* 11:41-45 (2000)) genes.

In addition, since there is no common 5' region of sequence at the 5' ends of any of these cDNAs, it appears likely that each is generated from a different transcriptional start site. It has been previously demonstrated that several murine *Pde4a* transcripts, including PDE4A5, are generated in this manner (Olsen & Bolger, *Mammalian Genome* 11:41-45 (2000)).

All references, publications, patents, patent applications, and commercial materials cited in this application are hereby incorporated by reference in their entirety.

7. Examples:

The following example is given to illustrate an embodiment which has been made within the scope of the present invention. It is to be understood that the following example is neither comprehensive nor exhaustive of the many types of embodiments which can be prepared in accordance with the present invention.

Example 1—Two Novel PDE4B Isoforms

Experimental Techniques:

Materials: A rat (*Rattus norvegicus*; Sprague-Dawley strain) cerebral cortex cDNA library, cloned into the Eco RI site of Lambda ZAPII, was obtained from Stratagene. All molecular biology, biochemistry and cell culture reagents were from New England Biolabs, Life Technologies or Roche Molecular Systems unless specified otherwise.

Isolation and Analysis of cDNA Clones: Procedures were as described by Sambrook *et al.* (Sambrook et al., *Molecular Cloning: A Laboratory Manual*, (1989)) unless otherwise specified. The cDNA library was screened with a probe corresponding to nucleotides 204 to 1299 of rat PDE4B3 (pRPDE74 (SEQ ID NO: 9) GenBank™ accession number U95748; (Huston et al., *Biochem J.* 328:549–56 (1997)). This region encodes the unique amino-terminal region of PDE4B3 as well as UCR1 and the majority of UCR2 (Fig. 1). Hybridization was performed with a final wash in 0.3 x SSC, 0.3% SDS at 62°C. Sequencing was performed on both strands with an ABI Prism sequencer (Perkin-Elmer) according to the manufacturer's instructions. Alignments were generated with the Gap and Lineup programs of the Wisconsin Package of UNIX sequence software programs (Oxford Molecular Group).

Results:

To obtain cDNAs encoding PDE4B isoforms, a rat cortex cDNA library was screened with a probe corresponding to UCR1 and UCR2 of rat PDE4B3 (Huston et al., *Biochem. J.* 328:549–56 (1997)). This probe was designed to detect all "long" (i.e., UCR1-containing) PDE4B isoforms. cDNAs encoding two different PDE4B isoforms were detected in the screen (see Fig. 1). One cDNA clone, called pRPDE89 (SEQ ID NO: 5), encoded a protein of 736 amino acids (SEQ ID NO: 6). This isoform was identical in length and had greater than 96% amino acid identity (712/736 amino acids identical, Fig. 2) with the human PDE4B1 isoform (SEQ ID NO: 7). Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993). It was therefore concluded that pRPDE89 encodes the rat PDE4B1 isoform.

Also detected in the screen was a cDNA clone, called pRPDE90 (SEQ ID NO: 1), which encoded the complete open reading frame of a novel PDE4B isoform. This new isoform was called PDE4B4, using the accepted nomenclature. Beavo, *Physiol. Rev.* 75:725–48 (1995). The PDE4B4 protein consists of 659 amino acids (SEQ ID NO: 2), 17

of which are located at the extreme amino-terminal end of the protein and show no detectable homology to any previously cloned PDE4B sequence (SEQ ID NOS: 3, 4). The remaining 642 amino acids are identical to the corresponding regions of the "long" PDE4B isoforms PDE4B1 and PDE4B3 (Fig. 3). The nucleotide sequences of the common regions of PDE4B1, PDE4B3 and PDE4B4 are also identical. The sequence of the novel region of PDE4B4 was confirmed by the sequence of another clone isolated in the screen, called pRPDE92 (SEQ ID NO: 10), which completely overlapped the novel region of pRPDE90 and contained sequence of an additional portion of the 5' untranslated region of the mRNA.

The invention may be embodied in other specific forms without departing from its essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes that come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS:

1. An isolated and purified nucleic acid molecule comprising nucleotides encoding the amino acid sequence of SEQ ID NO: 2.
2. The nucleic acid molecule of Claim 1, comprising nucleotides 262 to 2238 of SEQ
5 ID NO: 1.
3. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is subcloned into a plasmid.
4. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is subcloned into a prokaryotic or eukaryotic expression vector.
- 10 5. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is stably or transiently incorporated into a prokaryotic or eukaryotic host cell.
6. An isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 2.
- 15 7. An isolated and purified nucleic acid molecule comprising nucleotides which code for the amino acid sequence of SEQ ID NO: 4.
8. The nucleic acid molecule of Claim 7, comprising the nucleotide sequence of SEQ ID NO: 3.
16. 9. An isolated and purified nucleic acid molecule comprising a nucleotide sequence that encodes an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 4.
- 20 10. An isolated and purified nucleic acid molecule comprising a nucleotide sequence that encodes an amino acid sequence that is at least 75% identical to the amino acid sequence of SEQ ID NO: 4.
11. 11. An isolated and purified peptide comprising the amino acid sequence of SEQ ID NO: 4.
- 25 12. An antibody that specifically recognizes the peptide of claim 11.
13. An isolated and purified nucleic acid molecule comprising nucleotides encoding the amino acid sequence of SEQ ID NO: 6.
14. The nucleic acid molecule of Claim 13, comprising nucleotide 325 to 2532 of SEQ ID NO: 5.
- 30 15. The nucleic acid molecule of Claim 13, wherein said nucleic acid molecule is subcloned into a plasmid.
16. The nucleic acid molecule of Claim 13, wherein said nucleic acid molecule is

subcloned into a prokaryotic or eukaryotic expression vector.

17. The nucleic acid molecule of Claim 14, wherein said nucleic acid molecule is stably or transiently incorporated into a prokaryotic or eukaryotic host cell.

18. An isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 6.

5

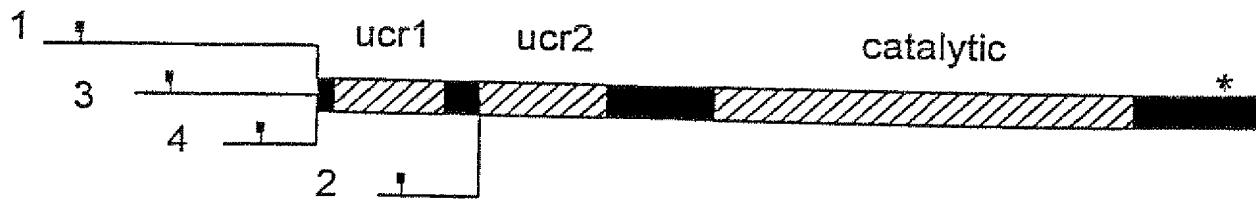


Fig. 2 (two pages in length)

1 MKKSRSVMTVMADDNVKDYFECSSL SKSYSSSNTLGIDLWRGRCCSGNL 50
||||| ||||| .|||||.||||||||||||| ||||| |||||
1 MKKSRSVMAVTADDNLKDYFECSSL SKSYSSSYTLGIDLWRGRCCSGNL 50

51 QLPPPLSQRQSERARTPEGDGISRPTTLPPLT LPSIAITV S QECFDVENG 100
||||| ||||| .|||||.||||||||||||| ||||| |||||
51 QLPPPLSQRQSERARTPEGDGISRPTTLPPLT LPSIAITV S QECFDVENG 100

101 PSPGRSPLDPQASSSAGLVLHATFPGHSQRRESFLYRSDSDYDLSPKAMS 150
||||| ||||| .|||||.||||||||||||| ||||| |||||
101 PSPGRSPLDPQASSSSGLVLHAAFPGHSQRRESFLYRSDSDYDLSPKAMS 150

151 RNSSLPSEQHGDDLIVTPFAQVLASLR SVRNNFTILT NLHGTSNKRSPAA 200
||||| ||||| .|||||.||||||||||||| :||||| .|||||
151 RNSSLPSEQHGDDLIVTPFAQVLASLR SVRNNFTLLTNLHGAPNKRSPAA 200

201 SQPPVSRVNPQEESYQKLAMETLEELDWCL DQLETIQT YRSVSEMASNKF 250
|| .||. .||||| .||||| .||||| .||||| .|||||
201 SQAPVTRVSLQEESYQKLAMETLEELDWCL DQLETIQT YRSVSEMASNKF 250

251 KRMLNRELTHLSEMSRSGNQVSEYISNTFLDKQNDVEIPSPTQKDREKKK 300
||||| ||||| .||||| .||||| .||||| .||||| .|||||
251 KRMLNRELTHLSEMSRSGNQVSEYISNTFLDKQNDVEIPSPTQKDREKKK 300

301 KQQLMTQISGVKKLMHSSSLNNTSISRGVN TENE DHLAKELEDLNKGWL 350
||||| ||||| .||||| .||||| .||||| .||||| .|||||
301 KQQLMTQISGVKKLMHSSSLNNTSISRGVN TENE DHLAKELEDLNKGWL 350

351 NIFNVAGYSHNRPLTCIMYAI FQERDLLKTFRISSDTFITYMMTLEDHYH 400
||||| .||||| .||||| .||||| .||||| .||||| .|||||
351 NIFNVAGYSHNRPLTCIMYAI FQERDLLKTFKISSDTFVTYMMTLEDHYH 400

401 SDVAYHNSLHAADVAQSTHVL LSTPALDAVFTDLEILAAIFAAAHDVDH 450
||||| .||||| .||||| .||||| .||||| .||||| .|||||
401 SDVAYHNSLHAADVAQSTHVL LSTPALDAVFTDLEILAAIFAAAHDVDH 450

451 PGVSNQFLINTNSELALMYNDESVLENHHAVGFKLLQEEHCDIFMNLTK 500
||||| .||||| .||||| .||||| .||||| .||||| .|||||
451 PGVSNQFLINTNSELALMYNDESVLENHHAVGFKLLQEEHCDIFQNLTK 500

501 KQRQLRKMVIDMVLATDM SKHMSLLADLKTMVETKKVTSSGVLLLDNYT 550
||||| .||||| .||||| .||||| .||||| .||||| .|||||
501 KQRQLRKMVIDMVLATDM SKHMSLLADLKTMVETKKVTSSGVLLLDNYT 550

551 DRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEEFFQQGDKERERGMEI 600
||||| .||||| .||||| .||||| .||||| .||||| .|||||
551 DRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEEFFQQGDKERERGMEI 600

601 SPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDLEDNRN 650
|||||
601 SPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDLEDNRN 650
|||||
651 WYQSMIPQSPSPPLDEQRDCQGLMEKFQFELTLDEEDSEGPEKEGEGHs 700
|||||
651 WYQSMIPQSPSPPLDERSRDCQGLMEKFQFELTLEEDSEGPEKEGEGPn 700
|||||
701 YFSSTKTLCVIDPENRDSLGETDIDIATEDKSPVDT* 736
|||||
701 YFSSTKTLCVIDPENRDSLEETDIDIATEDKSLIDT* 736

Fig. 3 (two pages in length)

PDE4B3	MTAKN SSKELPASES	EVCIKTFKEQ	MRLELELPKL
PDE4B1	MKKSRSVMAV	TADDNLKDYF	ECSLSKSYSS	SSYTLGIDLW	RGRCCSGNL
PDE4B4
PDE4B2
51					
PDE4B3	PGNRPTSPKI	SPRSSPRNSP	CFFRKLLVNK	SIRORRRTV	AHTCFDVENG
PDE4B1	QLPPLSQRQS	ERARTPEGDG	ISRPTTLPLT	TLPSIAITTV	SQEFCFDVENG
PDE4B4	MLH	VNDLPPPWRH SWICFDVENG
PDE4B2
101					
PDE4B3	PSPGRSPLDP	QASSSSGLVL	HAAPGHSQR	RESFLYRSDS	DYDLSPKAMS
PDE4B1	PSPGRSPLDP	QASSSSGLVL	HAAPGHSQR	RESFLYRSDS	DYDLSPKAMS
PDE4B4	PSPGRSPLDP	QASSSSGLVL	HAAPGHSQR	RESFLYRSDS	DYDLSPKAMS
PDE4B2
151					
PDE4B3	RNSSLPSEQH	GDDLIVTPFA	QVLASLRIVR	NNFTLLTNLH	GAPNKRSPAA
PDE4B1	RNSSLPSEQH	GDDLIVTPFA	QVLASLRSRV	NNFTLLTNLH	GAPNKRSPAA
PDE4B4	RNSSLPSEQH	GDDLIVTPFA	QVLASLRSRV	NNFTLLTNLH	GAPNKRSPAA
PDE4B2	MKEQGGTV	SGAGSSRGGG	DSAMASLQPL
201					
PDE4B3	SQAPVTRVSL	QEESYQKLAM	ETLEELDWCL	DQLETIQTYSR	SVSEMASNKF
PDE4B1	SQAPVTRVSL	QEESYQKLAM	ETLEELDWCL	DQLETIQTYSR	SVSEMASNKF
PDE4B4	SQAPVTRVSL	QEESYQKLAM	ETLEELDWCL	DQLETIQTYSR	SVSEMASNKF
PDE4B2	QPNYLSVCLF	AEESYQKLAM	ETLEELDWCL	DQLETIQTYSR	SVSEMASNKF
251					
PDE4B3	KRMLNRELTH	LSEMSRSGNQ	VSEYISNTFL	DKQNDVEIPS	PTQKDREKKK
PDE4B1	KRMLNRELTH	LSEMSRSGNQ	VSEYISNTFL	DKQNDVEIPS	PTQKDREKKK
PDE4B4	KRMLNRELTH	LSEMSRSGNQ	VSEYISNTFL	DKQNDVEIPS	PTQKDREKKK
PDE4B2	KRMLNRELTH	LSEMSRSGNQ	VSEYISNTFL	DKQNDVEIPS	PTQKDREKKK
301					
PDE4B3	KQQLMTQISG	VKKLMHSSSL	NNTSISRGFGV	NTENEDHLAK	ELEDLNWKGL
PDE4B1	KQQLMTQISG	VKKLMHSSSL	NNTSISRGFGV	NTENEDHLAK	ELEDLNWKGL
PDE4B4	KQQLMTQISG	VKKLMHSSSL	NNTSISRGFGV	NTENEDHLAK	ELEDLNWKGL
PDE4B2	KQQLMTQISG	VKKLMHSSSL	NNTSISRGFGV	NTENEDHLAK	ELEDLNWKGL
351					
PDE4B3	NIFNVAGYSH	NRPLTCIMYA	IFQERDPLLKT	FKIISSDTFVT	YMMTLEDHYH
PDE4B1	NIFNVAGYSH	NRPLTCIMYA	IFQERDPLLKT	FKIISSDTFVT	YMMTLEDHYH
PDE4B4	NIFNVAGYSH	NRPLTCIMYA	IFQERDPLLKT	FKIISSDTFVT	YMMTLEDHYH
PDE4B2	NIFNVAGYSH	NRPLTCIMYA	IFQERDPLLKT	FKIISSDTFVT	YMMTLEDHYH
401					
PDE4B3	SDVAYHNSLH	AADVAQSTHV	LLSTPALDAV	FTDLEILAAI	FAAAIHVDWH
PDE4B1	SDVAYHNSLH	AADVAQSTHV	LLSTPALDAV	FTDLEILAAI	FAAAIHVDWH
PDE4B4	SDVAYHNSLH	AADVAQSTHV	LLSTPALDAV	FTDLEILAAI	FAAAIHVDWH
PDE4B2	SDVAYHNSLH	AADVAQSTHV	LLSTPAPDAV	FTDLEILAAI	FAAAIHVDWH
451					
PDE4B3	PGVSNOFLIN	TNSELALMYN	DESVLENHHL	AVGFKLLOEE	HCDIFQNLTK
PDE4B1	PGVSNOFLIN	TNSELALMYN	DESVLENHHL	AVGFKLLOEE	HCDIFQNLTK
PDE4B4	PGVSNOFLIN	TNSELALMYN	DESVLENHHL	AVGFKLLOEE	HCDIFQNLTK
PDE4B2	PGVSNOFLIN	TNSELALMYN	DESVLENHHL	AVGFKLLOEE	HCDIFQNLTK

	501	
PDE4B3	KQRQTLRKMV IDMVLATDMS KHMSLLADLK TMVETKKVTS SGVLLLDNYT	550
PDE4B1	KQRQTLRKMV IDMVLATDMS KHMSLLADLK TMVETKKVTS SGVLLLDNYT	
PDE4B4	KQRQTLRKMV IDMVLATDMS KHMSLLADLK TMVETKKVTS SGVLLLDNYT	
PDE4B2	KQRQTLRKMV IDMVLATDMS KHMSLLADLK TMVETKKVTS SGVLLLDNYT	
	551	
PDE4B3	DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGM	600
PDE4B1	DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGM	
PDE4B4	DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGM	
PDE4B2	DRIQVLRNMV HCADLSNPTK SLELYRQWTD RIMEEFFQQG DKERERGM	
	601	
PDE4B3	SPMCDKHTAS VEKSQVGFI YIVHPLWETW ADLVQPDAQD ILDTLEDNRN	650
PDE4B1	SPMCDKHTAS VEKSQVGFI YIVHPLWETW ADLVQPDAQD ILDTLEDNRN	
PDE4B4	SPMCDKHTAS VEKSQVGFI YIVHPLWETW ADLVQPDAQD ILDTLEDNRN	
PDE4B2	SPMCDKHTAS VEKSQVGFI YIVHPLWETW ADLVQPDAQD ILDTLEDNRN	
	651	
PDE4B3	WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEDSE GPEKEGEGP	700
PDE4B1	WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEDSE GPEKEGEGP	
PDE4B4	WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEDSE GPEKEGEGP	
PDE4B2	WYQSMIPQSP SPPLDERSRD CQGLMEKFQF ELTLEEDSE GPEKEGEGP	
	701	
PDE4B3	YFSSTKTLCV IDPENRDSLE ETDIDIA KSLIDT*	736
PDE4B1	YFSSTKTLCV IDPENRDSLE ETDIDIA KSLIDT*	
PDE4B4	YFSSTKTLCV IDPENRDSLE ETDIDIA KSLIDT*	
PDE4B2	YFSSTKTLCV IDPENRDSLE ETDIDIA KSLIDT*	

Fig. 4

GAATTCCGCACGAGCAATTCCATCTGATTCTAAAGGAAGCTACTTGCATGGCCTCTGCAACCTC
GTGTGTCGATTGCTAAGTCATTGCTACTCGCATTGGATGATCTACCCCGCAATGGAGAGTGGCATGC
CATCAGAAAGAAAACGAACGGACAAAGAGGCTCAGTAGAAACTCTGGCAGCGAGAACACAGAGAAACGCA
TGGAGATGAGCTAAGTCGCTAGCGGTGGGCTGACAGTGTACCGGTTCAAGGATGTTGCACGTGAACGACT
TGCCTCCTCCCAGGCCACACTCGTGGATATGCTTGATGTGGAAATGGCCCTCTCCAGGTGGAGGCC
ACTGGACCCCAAGCCAGCTCTTCAGGACTGGTACTTCATGCCGCTTCCCTGGGACAGCCAACGCC
AGAGAGTCTTCTACAGATCCGACAGCGACTATGACTTGTCAACAAAAGCGATGTCAAGGAACCTCCT
CACTTCCCAGCGAACAAACACGGCGATGACTGATTGTCACTCCTTGTGCCAGGTTGTGCCAGCTTGCG
AAGCGTAAGAAACAATTTCACCCCTGTCGACAAACCTCACGGAGCACCGAACAGAGGTCGCCAGCGGCT
AGTCAGGCTCCAGTCACCAGAGTCAGCTGCAAGAAGAATCATATCAGAAACTAGCAATGGAGACGCTGG
AGGAACCTAGACTGGTGCCTAGACCAGCTAGAGACCATCCAGACCTACCGCTCTGTCAGCGAGATGGCTTC
AAACAAGTTCAAAAGGATGCTGAACCGGGAGCTGACACACCTCTCAGAGATGAGCAGATCAGGGAACCAA
GTGTCTGAATACATTGAAACACGTTCTTAGACAAGCAGAACAGATGTGGAAATCCCATCTCCACCCAGA
AGGACAGGGAGAAGAAGAAGCAGCAGCTCATGACCCAGATAAGTGGAGTGAAGAAACTGATGCACAG
CTCAAGCCTGAACAACACAAGCATCTCACGCTTGGAGTCAACACGGAAAATGAGGATCATCTAGCCAAG
GAGCTGGAAGACCTGAACAAATGGGCCCTAACATCTCAACGCTGGTACTCCATAATCGGCCCC
TCACATGCATCATGTACGCCATTTCAGGAAAGAGACCTCTAAAGACGTTAAAATCTCCTCCGACAC
CTTCGTAACCTACATGATGACTTAAAGAGACCATTCATTCTGATGTGGCTATCACAAACAGCCTGCAC
GCTGCTGACGTGGCCACTCAACGCACGTTCTCCTCTACGCCAGCAGCTGGATGCTGTCTCACAGACC
TGGAAATCTGGCTGCCATTTCAGCTGCCATCCATGATGTGATCATCCTGGAGTCTCAATCAGTT
TCTCATCAATACAAATTCCGAACTTGCTTGATGTATAATGACAATCTGTGCTGGAAAACCATCACCTC
GCTGTGGGATTCAAGCTCCCAAGAGGAACATTGGACATCTTCAAGAATCTTACCAAGAAGCAACGCC
AGACACTCAGGAAAATGGTATTGACATGGTGTAGCAACTGATATGTCCAAGCACATGAGCCTCTGGC
TGACCTTAAACGATGGTAGAAACCAAAAGGTGACGAGCTCCGGTGTCTCCTCTGGACAACATACT
GACCGGATAAGGTTCTCGAACATGGTACATTGTGAGACCTGAGCAACCTACCAAGTCTGGAGT
TGTATCGGAAATGGACTGATGCATCATGGAGGAGTTTCCAACAGGGAGACAAAGAACGGGAGAGGGG
AATGGAGATTAGCCAAATGTGTGATAAACACACAGCTCTGTGAAAAGTCCAGGTGGTTATTGAC
TACATTGTCCATCCATTGTGGGAGACCTGGCAGACCTGGTCTAGCTGATGCTCAAGACATTGGACA
CACTAGAAGATAACAGGAACCTGGTACCGAGAATGATTCCCCAGAGCCCCCTCTCACCAGGGAGAG
GAGCAGGGACTGCCAAGGCCATTGGAGAAGTTCACTGAACTGACCTTGAAGAAGAGGATTCTGAA
GGACCGGAAAAGGAGGGAGAAGGCCCAACTATTTCAGCAGCACAAGACACTTGTGTGATCGATCCAG
AGAACAGGGATTCTCTGGAAAGAGACTGACATAGACATTGCCACAGAACAGTCTGATCGACACATA
ATCTCCCTCTGTGTGGAGGTGAACATTCTATCCTTGACGAGCATGCCAGCTGAGTGGTAGGGCCCACCTA
CCAGAGCCAAGGCCCTGCACAAACAAAGGCCACCTGGCTTGCAGTTACTGAGTTGGAGGCCAGAATGC
AAGGCCGTGAAGCAAATAGCAGTCCGTGCTGCCATTGCCGGAGCTT1

Fig. 5

GAATTCCGGCACGAGGCAGGGCGGGGGCGGGCGGTAGTGGCAGACGGCCGCAGGGATTATGAATGGGG
GTGGGGGCCGGCAGTTGAGGTTCCACCCGGATCGTCCGCACCGCTGATGGCACGCAGGGCTGCGTG
TAATCCTCCAGCCTCGGTGGAGGGAGGCTGCAGCGAGCGCCGGCTGGCAGTAAGGGTTCTCTGC
TCCCCTGCAGGTTGCAGCGCTGGAGTGCAGGGAGCTGGCCAGGTCTAGTCTGCAGTCAGCAAAGCTGCA
GCAAACAGCAGACATCTCCAGAGGAGCTGTTGCCACATCTATAATGAAGAAAAGTAGGAGTGTGATGGC
CGTGAUTGCAAGATGATAATCTAAGGACTATTTGAATGTAGCTTGAGTAAATCTACAGTTCTCCAGT
TATACCCCTGGGATTGACCTCTGGAGAGGCAGAAGGTGCTGTTAGGAAACTACAGTTGCCACCATTGT
CCCAGAGACAAAGTGAAGGGCAAGGACACCTGAGGGAGATGGCATTCCAGGCCAACACGCTACCTTT
GACGACACTTCCCAGCATTGCTATAACAACGTAAAGCAGGAGTGCTTGATGTGAAAATGGCCCTTCT
CCAGGTCGGAGCCCACGGACCTCAAGCCAGCTCTTCAGGACTGGTACTTCATGCCGCTTCCCTG
GGCACAGCCAACGCAGAGAGTCTTCTACAGATCCGACAGCGACTATGACTTGTCACTCCTTGC
GTCAAGGAACCTCTCACTTCCCAGCGAACACACGGCGATGACTGATTGTCACTCCTTGC
CTTGCCAGCTTGCAGCGTAAGAAACAATTTCACCCCTGCTGACAAACCTCACGGAGCACC
GGTGCAGCGGCTAGTCAGGCTCAGTCACCAGAGTCAGCCTGCAAGAAGAATCATATCAGAAACTAGC
AATGGAGACGCTGGAGGAACTAGACTGGTCCTAGACCAGCTAGAGACCAC
AGCGAGATGGCTCAAACAAGTCAAAAGGATGCTGAACCGGGAGCTGACACAC
GATCAGGGAACCAAGTGTCTGAATACATTGCAACACGTTCTAGACAAGCAGAAC
GAGATGGAGTGAAG
ATCTCCCACCCAGAAGGACAGGGAGAAGAAGAAC
AAACTGATGCACAGCTCAAGCCTGAACAAACACAAGCATCTCAGGCT
ATCATCTAGGCAAGGAGCTGGAAAGACCTGAAACAAATGGGCCT
CCATAATCGCCCCCTCACATGCATCATGTA
ATCTCTCCGACACCTCGTAACCTACATGACTTGA
ACAACAGCCTGCACGCTGCTGACGTGGCCAGTCACG
TGTCTTCACAGACCTGGAAATCTGGCTGCCATT
GTCTCAATCAGTTCTCATCAA
AAACCATCACCTCGCTGTGGGATTCAAGCT
CAAGAAGCAACGCCAGACACTCAGG
ATGAGCCTCTGGCTGACCT
TGGACAAC
CAAGTC
AAAGGGAGAGGGAAATGGAGATTAG
TTGGTTCACTGACTACATTG
AGACATT
CCACTGGAC
AAGAGGACT
TGTGATCG
CTGATCG
GTAGGGCC
TTGGAGCC
CGGAGAC
GCTGAGAG
ATCTATAA
TGAAATGC
AAAAACCTGCAG

SEQUENCE LISTING

<110> Bolger, Graeme

<120> TWO NOVEL cAMP-SPECIFIC PHOSPHODIESTERASE (PDE4B) ISOFORMS AND RELATED TECHNOLOGY

<130> 1321.2.43

<150> 60/170,562

<151> 1999-12-14

<160> 11

<170> PatentIn version 3.0

<210> 1

<211> 2433

<212> DNA

<213> Rattus norvegicus

<220>

<221> CDS

<222> (262)..(2238)

<400> 1

gaattcggca cgagcaattt cctcatctga tttctaaagg aagctacttg cgatggtcct 60

ctgcaacctc gtgtgtcgat tgctaagtca ttgctactcg cattggaatg atctctaccc 120

cgcaatggag agtggcatgc catcagaaaag aaaaacgaac ggacaaaagag ctcagtagaa 180

actctggcag cgagaacaca gagaaacgca tggagatgag ctaagtcgct gagcggtggg 240

ctgacagtgt accggttcag g atg ttg cac gtg aac gac ttg cct cct ccc 291
Met Leu His Val Asn Asp Leu Pro Pro Pro
1 5 10agg cga cac tcg tgg ata tgc ttt gat gtg gaa aat ggc cct tct cca 339
Arg Arg His Ser Trp Ile Cys Phe Asp Val Glu Asn Gly Pro Ser Pro
15 20 25ggc cgg agc cca ctg gac cct caa gcc agc tct tct tca gga ctg gta 387
Gly Arg Ser Pro Leu Asp Pro Gln Ala Ser Ser Ser Gly Leu Val
30 35 40ctt cat gcc gcc ttc cct ggg cac agc caa cgc aga gag tct ttt ctc 435
Leu His Ala Ala Phe Pro Gly His Ser Gln Arg Arg Glu Ser Phe Leu
45 50 55tac aga tcc gac agc gac tat gac ttg tca cca aaa gcg atg tca agg 483
Tyr Arg Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg
60 65 70aac tcc tca ctt ccc agc gaa caa cac ggc gat gac ctg att gtc act 531
Asn Ser Ser Leu Pro Ser Glu Gln His Gly Asp Asp Leu Ile Val Thr
75 80 85 90cct ttt gcc cag gtt ctt gcc agc ttg cga agc gta aga aac aat ttc 579
Pro Phe Ala Gln Val Leu Ala Ser Leu Arg Ser Val Arg Asn Asn Phe
95 100 105

acc ctg ctg aca aac ctt cac gga gca ccg aac aag agg tcg cca gcg 627
 Thr Leu Leu Thr Asn Leu His Gly Ala Pro Asn Lys Arg Ser Pro Ala
 110 115 120

 gct agt cag gct cca gtc acc aga gtc agc ctg caa gaa gaa tca tat 675
 Ala Ser Gln Ala Pro Val Thr Arg Val Ser Leu Gln Glu Ser Tyr
 125 130 135

 cag aaa cta gca atg gag acg ctg gag gaa cta gac tgg tgc cta gac 723
 Gln Lys Leu Ala Met Glu Thr Leu Glu Leu Asp Trp Cys Leu Asp
 140 145 150

 cag cta gag acc atc cag acc tac cgc tct gtc agc gag atg gct tca 771
 Gln Leu Glu Thr Ile Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser
 155 160 165 170

 aac aag ttc aaa agg atg ctg aac cgg gag ctg aca cac ctc tca gag 819
 Asn Lys Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu
 175 180 185

 atg agc aga tca ggg aac caa gtg tct gaa tac att tcg aac acg ttc 867
 Met Ser Arg Ser Gly Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe
 190 195 200

 tta gac aag cag aac gat gtg gaa atc cca tct ccc acc cag aag gac 915
 Leu Asp Lys Gln Asn Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp
 205 210 215

 agg gag aag aag aag cag cag ctc atg acc cag ata agt gga gtg 963
 Arg Glu Lys Lys Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val
 220 225 230

 aag aaa ctg atg cac agc tca agc ctg aac aac aca agc atc tca cgc 1011
 Lys Lys Leu Met His Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg
 235 240 245 250

 ttt gga gtc aac acg gaa aat gag gat cat cta gcc aag gag ctg gaa 1059
 Phe Gly Val Asn Thr Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu
 255 260 265

 gac ctg aac aaa tgg ggc ctt aac atc ttc aac gtg gct ggg tac tcc 1107
 Asp Leu Asn Trp Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser
 270 275 280

 cat aat cgg ccc ctc aca tgc atc atg tac gcc att ttc cag gaa aga 1155
 His Asn Arg Pro Leu Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg
 285 290 295

 gac ctt cta aag acg ttt aaa atc tcc tcc gac acc ttc gta acc tac 1203
 Asp Leu Leu Lys Thr Phe Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr
 300 305 310

 atg atg act tta gaa gac cat tac cat tct gat gtg gcg tat cac aac 1251
 Met Met Thr Leu Glu Asp His Tyr His Ser Asp Val Ala Tyr His Asn
 315 320 325 330

 agc ctg cac gct gct gac gtg gcc cag tca acg cac gtt ctc ctc tct 1299
 Ser Leu His Ala Ala Asp Val Ala Gln Ser Thr His Val Leu Leu Ser
 335 340 345

acg cca gca ctg gat gct gtc ttc aca gac ctg gaa atc ctg gct gcc Thr Pro Ala Leu Asp Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala 350 355 360	1347
att ttt gca gct gcc atc cat gat gtt gat cat cct gga gtc tcc aat Ile Phe Ala Ala Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn 365 370 375	1395
cag ttt ctc atc aat aca aat tcc gaa ctt gct ttg atg tat aat gac Gln Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp 380 385 390	1443
gaa tct gtg ctg gaa aac cat cac ctc gct gtg gga ttc aag ctc ctt Glu Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu 395 400 405 410	1491
caa gag gaa cat tgc gac atc ttt cag aat ctt acc aag aag caa cgc Gln Glu Glu His Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg 415 420 425	1539
cag aca ctc agg aaa atg gtg att gac atg gtg tta gca act gat atg Gln Thr Leu Arg Lys Met Val Ile Asp Met Val Leu Ala Thr Asp Met 430 435 440	1587
tcc aag cac atg agc ctc ctg gct gac ctt aaa acg atg gta gaa acc Ser Lys His Met Ser Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr 445 450 455	1635
aaa aag gtg acg agc tcc ggt gtt ctc ctc ctg gac aac tat act gac Lys Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp 460 465 470	1683
cgg ata cag gtt ctt cgc aac atg gta cat tgt gca gac ctg agc aac Arg Ile Gln Val Leu Arg Asn Met Val His Cys Ala Asp Leu Ser Asn 475 480 485 490	1731
cct acc aag tcc ttg gag ttg tat cgg caa tgg act gat cgc atc atg Pro Thr Lys Ser Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met 495 500 505	1779
gag gag ttt ttc caa cag gga gac aaa gaa cgg gag agg gga atg gag Glu Glu Phe Phe Gln Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu 510 515 520	1827
att agc cca atg tgt gat aaa cac aca gct tct gtg gaa aag tcc cag Ile Ser Pro Met Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln 525 530 535	1875
gtt ggt ttc att gac tac att gtc cat cca ttg tgg gag acc tgg gca Val Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala 540 545 550	1923
gac ctg gtt cag cct gat gct caa gac att ttg gac aca cta gaa gat Asp Leu Val Gln Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp 555 560 565 570	1971
aac agg aac tgg tac cag agt atg att ccc cag agc ccc tct cca cca Asn Arg Asn Trp Tyr Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro 575 580 585	2019
ctg gac gag agg agc agg gac tgc caa ggc ctt atg gag aag ttt cag	2067

Leu Asp Glu Arg Ser Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln			
590	595	600	
tcc gaa ctg acc ctt gaa gag gat tct gaa gga ccg gaa aag gag		2115	
Phe Glu Leu Thr Leu Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu			
605	610	615	
gga gaa ggc ccc aac tat ttc agc agc aca aag aca ctt tgt gtg atc		2163	
Gly Glu Gly Pro Asn Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile			
620	625	630	
gat cca gag aac agg gat tct ctg gaa gag act gac ata gac att gcc		2211	
Asp Pro Glu Asn Arg Asp Ser Leu Glu Thr Asp Ile Asp Ile Ala			
635	640	645	650
aca gaa gac aag tct ctg atc gac aca taatctccct ctgtgtggag		2258	
Thr Glu Asp Lys Ser Leu Ile Asp Thr			
655			
gtgaacattc tatccttgac gagcatgcca gctgagtgggt agggcccacc taccagagcc		2318	
aaggcctgca caaaaacaaag gccacactggc tttgcagtta cttgagtttgc gagccagaat		2378	
gcaaggccgt gaagcaaata gcagttccgt gctgccttgc cttgccggcg agctt		2433	
<210> 2			
<211> 659			
<212> PRT			
<213> Rattus norvegicus			
<400> 2			
Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile			
1	5	10	15
Cys Phe Asp Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp			
20	25	30	
Pro Gln Ala Ser Ser Ser Gly Leu Val Leu His Ala Ala Phe Pro			
35	40	45	
Gly His Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp			
50	55	60	
Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser			
65	70	75	80
Glu Gln His Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu			
85	90	95	
Ala Ser Leu Arg Ser Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu			
100	105	110	

His Gly Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val
115 120 125

Thr Arg Val Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu
130 135 140

Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln
145 150 155 160

Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met
165 170 175

Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn
180 185 190

Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp
195 200 205

Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys
210 215 220

Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser
225 230 235 240

Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu
245 250 255

Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly
260 265 270

Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr
275 280 285

Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe
290 295 300

Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp
305 310 315 320

His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp
325 330 335

Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala
340 345 350

Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile

355

360

365

His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr
370 375 380

Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn
385 390 395 400

His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp
405 410 415

Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met
420 425 430

Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu
435 440 445

Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser
450 455 460

Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg
465 470 475 480

Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu
485 490 495

Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln
500 505 510

Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp
515 520 525

Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr
530 535 540

Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp
545 550 555 560

Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln
565 570 575

Ser Met Ile Pro Gln Ser Pro Ser Pro Leu Asp Glu Arg Ser Arg
580 585 590

Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu
595 600 605

Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr
610 615 620

Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp
625 630 635 640

Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu
645 650 655

Ile Asp Thr

<210> 3

<211> 51

<212> DNA

<213> Rattus norvegicus

<220>

<221> CDS

<222> (1)...(51)

<400> 3

atg ttg cac gtg aac gac ttg cct cct ccc agg cga cac tcg tgg ata
Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile
1 5 10 15

48

tgc
Cys

51

<210> 4

<211> 17

<212> PRT

<213> Rattus norvegicus

<400> 4

Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile
1 5 10 15

Cys

<210> 5

<211> 3022

<212> DNA

<213> Rattus norvegicus

<220>

<221> CDS

<222> (325)...(2532)

<400> 5
gaattcgca cgaggcgcgg gggcgaaaa ggcgtgttgtt ggcagacggc cgcaggatt 60
atgaatgggg gtggggggccg gcgagtttagt gttccaccccg ggatcgtccg caccggctga 120
tggcacgca gggctgcgtg taatcctcca gcctcggtgg agggaggctg cagcgagcgc 180
cggctggcag taagggttct tctgcaaaag tcccctgcgg ttgcgcgcgt ggagtgcggg 240
ggagctcggc caggtcttagt ctgcagtcag caaagctgca gcaaacagca gacatctcca 300
gaggagctgt ttgccacatc tata atg aag aaa agt agg agt gtg atg gcc 351
Met Lys Lys Ser Arg Ser Val Met Ala
1 5
gtg act gca gat gat aat ctt aag gac tat ttt gaa tgt agc ttg agt 399
Val Thr Ala Asp Asp Asn Leu Lys Asp Tyr Phe Glu Cys Ser Leu Ser
10 15 20 25
aaa tcc tac agt tct tcc agt tat acc ctt ggg att gac ctc tgg aga 447
Lys Ser Tyr Ser Ser Ser Tyr Thr Leu Gly Ile Asp Leu Trp Arg
30 35 40
ggc aga agg tgc tgg tca gga aac tta cag ttg cca cca ttg tcc cag 495
Gly Arg Arg Cys Cys Ser Gly Asn Leu Gln Leu Pro Pro Leu Ser Gln
45 50 55
aga caa agt gaa agg gca agg aca cct gag gga gat ggc att tcc agg 543
Arg Gln Ser Glu Arg Ala Arg Thr Pro Glu Gly Asp Gly Ile Ser Arg
60 65 70
cca acc acg cta cct ttg acg aca ctt ccc agc att gct ata aca act 591
Pro Thr Thr Leu Pro Leu Thr Thr Leu Pro Ser Ile Ala Ile Thr Thr
75 80 85
gta agc cag gag tgc ttt gat gtg gaa aat ggc cct tct cca ggt cgg 639
Val Ser Gln Glu Cys Phe Asp Val Glu Asn Gly Pro Ser Pro Gly Arg
90 95 100 105
agc cca ctg gac cct caa gcc agc tct tct tca gga ctg gta ctt cat 687
Ser Pro Leu Asp Pro Gln Ala Ser Ser Ser Gly Leu Val Leu His
110 115 120
gcc gcc ttc cct ggg cac agc caa cgc aga gag tct ttt ctc tac aga 735
Ala Ala Phe Pro Gly His Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg
125 130 135
tcc gac agc gac tat gac ttg tca cca aaa gcg atg tca agg aac tcc 783
Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg Asn Ser
140 145 150
tca ctt ccc agc gaa caa cac ggc gat gac ctg att gtc act cct ttt 831
Ser Leu Pro Ser Glu Gln His Gly Asp Asp Leu Ile Val Thr Pro Phe
155 160 165
gcc cag gtt ctt gcc agc ttg cga agc gta aga aac aat ttc acc ctg 879
Ala Gln Val Leu Ala Ser Leu Arg Ser Val Arg Asn Asn Phe Thr Leu
170 175 180 185
ctg aca aac ctt cac gga gca ccg aac aag agg tcg cca gcg gct agt 927
Leu Thr Asn Leu His Gly Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser

190

195

200

cag gct cca gtc acc aga gtc agc ctg caa gaa gaa tca tat cag aaa Gln Ala Pro Val Thr Arg Val Ser Leu Gin Glu Glu Ser Tyr Gln Lys 205	210	215	975
cta gca atg gag acg ctg gag gaa cta gac tgg tgc cta gac cag cta Leu Ala Met Glu Thr Leu Glu Leu Asp Trp Cys Leu Asp Gln Leu 220	225	230	1023
gag acc atc cag acc tac cgc tct gtc agc gag atg gct tca aac aag Glu Thr Ile Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys 235	240	245	1071
tcc aaa agg atg ctg aac cgg gag ctg aca cac ctc tca gag atg agc Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser 250	255	260	1119
aga tca ggg aac caa gtg tct gaa tac att tcg aac acg ttc tta gac Arg Ser Gly Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp 270	275	280	1167
aag cag aac gat gtg gaa atc cca tct ccc acc cag aag gac agg gag Lys Gln Asn Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu 285	290	295	1215
aag aag aag aag cag cag ctc atg acc cag ata agt gga gtg aag aaa Lys Lys Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys 300	305	310	1263
ctg atg cac agc tca agc ctg aac aac aca agc atc tca cgc ttt gga Leu Met His Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly 315	320	325	1311
gtc aac acg gaa aat gag gat cat cta gcc aag gag ctg gaa gac ctg Val Asn Thr Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu 330	335	340	1359
aac aaa tgg ggc ctt aac atc ttc aac gtg gct ggg tac tcc cat aat Asn Lys Trp Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn 350	355	360	1407
cgg ccc ctc aca tgc atc atg tac gcc att ttc cag gaa aga gac ctt Arg Pro Leu Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu 365	370	375	1455
cta aag acg ttt aaa atc tcc tcc gac acc ttc gta acc tac atg atg Leu Lys Thr Phe Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met 380	385	390	1503
act tta gaa gac cat tac cat tct gat gtg gcg tat cac aac agc ctg Thr Leu Glu Asp His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu 395	400	405	1551
cac gct gct gac gtg gcc cag tca acg cac gtt ctc ctc tct acg cca His Ala Ala Asp Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro 410	415	420	1599
gca ctg gat gct gtc ttc aca gac ctg gaa atc ctg gct gcc att ttt Ala Leu Asp Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe 430	435	440	1647

gca gct gcc atc cat gat gtt gat cat cct gga gtc tcc aat cag ttt Ala Ala Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe 445 450 455	1695
ctc atc aat aca aat tcc gaa ctt gct ttg atg tat aat gac gaa tct Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser 460 465 470	1743
gtg ctg gaa aac cat cac ctc gct gtg gga ttc aag ctc ctt caa gag Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu 475 480 485	1791
gaa cat tgc gac atc ttt cag aat ctt acc aag aag caa cgc cag aca Glu His Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr 490 495 500 505	1839
ctc agg aaa atg gtg att gac atg gtg tta gca act gat atg tcc aag Leu Arg Lys Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys 510 515 520	1887
cac atg agc ctc ctg gct gac ctt aaa acg atg gta gaa acc aaa aag His Met Ser Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys 525 530 535	1935
gtg acg agc tcc ggt gtt ctc ctc ctg gac aac tat act gac cgg ata Val Thr Ser Ser Gly Val Leu Leu Asp Asn Tyr Thr Asp Arg Ile 540 545 550	1983
cag gtt ctt cgc aac atg gta cat tgt gca gac ctg agc aac cct acc Gln Val Leu Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr 555 560 565	2031
aag tcc ttg gag ttg tat cgg caa tgg act gat cgc atc atg gag gag Lys Ser Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu 570 575 580 585	2079
ttt ttc caa cag gga gac aaa gaa cgg gag agg gga atg gag att agc Phe Phe Gln Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser 590 595 600	2127
cca atg tgt gat aaa cac aca gct tct gtg gaa aag tcc cag gtt ggt Pro Met Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly 605 610 615	2175
ttc att gac tac att gtc cat cca ttg tgg gag acc tgg gca gac ctg Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu 620 625 630	2223
gtt cag cct gat gct caa gac att ttg gac aca cta gaa gat aac agg Val Gln Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg 635 640 645	2271
aac tgg tac cag agt atg att ccc cag agc ccc tct cca cca ctg gac Asn Trp Tyr Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp 650 655 660 665	2319
gag agg agc agg gac tgc caa ggc ctt atg gag aag ttt cag ttc gaa Glu Arg Ser Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu 670 675 680	2367

ctg acc ctt gaa gaa gag gat tct gaa gga ccg gaa aag gag gga gaa Leu Thr Leu Glu Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu 685 690 695	2415
ggc ccc aac tat ttc agc agc aca aag aca ctt tgt gtg atc gat cca Gly Pro Asn Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro 700 705 710	2463
gag aac agg gat tct ctg gaa gag act gac ata gac att gcc aca gaa Glu Asn Arg Asp Ser Leu Glu Thr Asp Ile Asp Ile Ala Thr Glu 715 720 725	2511
gac aag tct ctg atc gac aca taatctccct ctgtgtggag gtgaacattc Asp Lys Ser Leu Ile Asp Thr 730 735	2562
tatccttgac gagcatgccca gctgagtggt agggcccacc taccagagcc aaggcctgca caaaaacaag gccacactggc ctttgcagtt acttgagttt ggagccagaa tgcaaggccg tgaagcaaat agcagttccg tgctgccttg cttgccggc gagcttggcg gagacccgca gctgttagtag aagccagttc ccagcacagc taaatggctt gaaaacagag gacagaaagc tgagagattt ctctgcaata ggtgttgagg ggctgtcccg acaggtgact gaactcacta acaacttcat ctataaatct cacccatccct gttgtctgcc aacctgtgtg ccttttttgt aaaatgtttt cgtgtctttg aaatgcctgt tgaatatcta gagtttagta ctccttcta caaactttt tgagtcttcc tggaaaaaaa aaacctgcag	2622 2682 2742 2802 2862 2922 2982 3022

<210> 6
<211> 736
<212> PRT
<213> Rattus norvegicus

<400> 6

Met Lys Lys Ser Arg Ser Val Met Ala Val Thr Ala Asp Asp Asn Leu 1 5 10 15
--

Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser Tyr Ser Ser Ser 20 25 30

Tyr Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg Arg Cys Cys Ser Gly 35 40 45

Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln Ser Glu Arg Ala Arg 50 55 60

Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr Thr Leu Pro Leu Thr 65 70 75 80
--

Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser Gln Glu Cys Phe Asp

85

90

95

Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln Ala
100 105 110

Ser Ser Ser Ser Gly Leu Val Leu His Ala Ala Phe Pro Gly His Ser
115 120 125

Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Leu
130 135 140

Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln His
145 150 155 160

Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu
165 170 175

Arg Ser Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu His Gly Ala
180 185 190

Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val Thr Arg Val
195 200 205

Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu Glu
210 215 220

Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr Arg
225 230 235 240

Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn Arg
245 250 255

Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser
260 265 270

Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu Ile
275 280 285

Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Gln Gln Leu
290 295 300

Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu
305 310 315 320

Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu Asp
325 330 335

His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn Ile
340 345 350

Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile Met
355 360 365

Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile Ser
370 375 380

Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp His Tyr His
385 390 395 400

Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala Gln
405 410 415

Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe Thr
420 425 430

Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp Val
435 440 445

Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
450 455 460

Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
465 470 475 480

Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Gln
485 490 495

Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp
500 505 510

Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp
515 520 525

Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
530 535 540

Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val
545 550 555 560

His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg
565 570 575

Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys
 580 585 590

Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr
 595 600 605

Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
 610 615 620

Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp
 625 630 635 640

Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile
 645 650 655

Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg Asp Cys Gln
 660 665 670

Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Glu Asp
 675 680 685

Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr Phe Ser Ser
 690 695 700

Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Glu
 705 710 715 720

Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu Ile Asp Thr
 725 730 735

<210> 7

<211> 736

<212> PRT

<213> Homo sapiens

<400> 7

Met Lys Lys Ser Arg Ser Val Met Thr Val Met Ala Asp Asp Asn Val
 1 5 10 15

Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser Tyr Ser Ser Ser Ser
 20 25 30

Asn Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg Arg Cys Cys Ser Gly
 35 40 45

Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln Ser Glu Arg Ala Arg
 50 55 60

Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr Thr Leu Pro Leu Thr

65	70	75	80
Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser Gln Glu Cys Phe Asp			
85		90	95
Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln Ala			
100		105	110
Ser Ser Ser Ala Gly Leu Val Leu His Ala Thr Phe Pro Gly His Ser			
115		120	125
Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Leu			
130		135	140
Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln His			
145		150	155
Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu			
165		170	175
Arg Ser Val Arg Asn Asn Phe Thr Ile Leu Thr Asn Leu His Gly Thr			
180		185	190
Ser Asn Lys Arg Ser Pro Ala Ala Ser Gln Pro Pro Val Ser Arg Val			
195		200	205
Asn Pro Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu Glu			
210		215	220
Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr Arg			
225		230	235
240			
Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn Arg			
245		250	255
Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser			
260		265	270
Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu Ile			
275		280	285
Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Gln Gln Leu			
290		295	300
Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu			
305		310	315
320			
Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu Asp			
325		330	335
His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn Ile			
340		345	350
Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile Met			
355		360	365
Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Arg Ile Ser			
370		375	380
Ser Asp Thr Phe Ile Thr Tyr Met Met Thr Leu Glu Asp His Tyr His			
385		390	395
400			

Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala Gln
 405 410 415
 Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe Thr
 420 425 430
 Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp Val
 435 440 445
 Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
 450 455 460
 Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
 465 470 475 480
 Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Met
 485 490 495
 Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp
 500 505 510
 Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp
 515 520 525
 Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
 530 535 540
 Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val
 545 550 555 560
 His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg
 565 570 575
 Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys
 580 585 590
 Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr
 595 600 605
 Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
 610 615 620
 Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp
 625 630 635 640
 Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile
 645 650 655
 Pro Gln Ser Pro Ser Pro Leu Asp Glu Gln Asn Arg Asp Cys Gln
 660 665 670
 Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Asp Glu Glu Asp
 675 680 685
 Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly His Ser Tyr Phe Ser Ser
 690 695 700
 Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Gly
 705 710 715 720

Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Pro Val Asp Thr
 725 730 735

<210> 8
 <211> 564
 <212> PRT
 <213> Rattus norvegicus

<400> 8

Met Lys Glu Gln Gly Gly Thr Val Ser Gly Ala Gly Ser Ser Arg Gly
 1 5 10 15

Gly Gly Asp Ser Ala Met Ala Ser Leu Gln Pro Leu Gln Pro Asn Tyr
 20 25 30

Leu Ser Val Cys Leu Phe Ala Glu Glu Ser Tyr Gln Lys Leu Ala Met
 35 40 45

Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile
 50 55 60

Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg
 65 70 75 80

Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly
 85 90 95

Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn
 100 105 110

Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys
 115 120 125

Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His
 130 135 140

Ser Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr
 145 150 155 160

Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp
 165 170 175

Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu
 180 185 190

Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr
 195 200 205

Phe Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu
 210 215 220

Asp His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala
 225 230 235 240

Asp Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp
 245 250 255

Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala
 260 265 270

Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn
 275 280 285

Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu
 290 295 300

Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys
 305 310 315 320

Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys
 325 330 335

Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser
 340 345 350

Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser
 355 360 365

Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu
 370 375 380

Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu
 385 390 395 400

Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln
 405 410 415

Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys
 420 425 430

Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp
 435 440 445

Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro
 450 455 460

Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr
 465 470 475 480

Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser
 485 490 495

Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu
 500 505 510

Glu Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn
 515 520 525

Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg
 530 535 540

Asp Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser
 545 550 555 560

Leu Ile Asp Thr

<210> 9
 <211> 721
 <212> PRT
 <213> Rattus norvegicus

<400> 9

Met Thr Ala Lys Asn Ser Ser Lys Glu Leu Pro Ala Ser Glu Ser Glu
1 5 10 15

Val Cys Ile Lys Thr Phe Lys Glu Gln Met Arg Leu Glu Leu Glu Leu
20 25 30

Pro Lys Leu Pro Gly Asn Arg Pro Thr Ser Pro Lys Ile Ser Pro Arg
35 40 45

Ser Ser Pro Arg Asn Ser Pro Cys Phe Phe Arg Lys Leu Leu Val Asn
50 55 60

Lys Ser Ile Arg Gln Arg Arg Arg Phe Thr Val Ala His Thr Cys Phe
65 70 75 80

Asp Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln
85 90 95

Ala Ser Ser Ser Ser Gly Leu Val Leu His Ala Ala Phe Pro Gly His
100 105 110

Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp
115 120 125

Leu Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln
130 135 140

His Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser
145 150 155 160

Leu Arg Ile Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu His Gly
165 170 175

Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val Thr Arg
180 185 190

Val Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu
195 200 205

Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr
210 215 220

Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn
225 230 235 240

Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val
245 250 255

Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu
260 265 270

Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Gln Gln
275 280 285

Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser
290 295 300

Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu

305	310	315	320
Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn			
325		330	335
Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile			
340		345	350
Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile			
355		360	365
Ser Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp His Tyr			
370		375	380
His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala			
385		390	395
Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe			
405		410	415
Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp			
420		425	430
Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser			
435		440	445
Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His			
450		455	460
Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe			
465		470	475
Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile			
485		490	495
Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala			
500		505	510
Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val			
515		520	525
Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met			
530		535	540
Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr			
545		550	555
Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp			
565		570	575
Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His			
580		585	590
Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val			
595		600	605
His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln			
610		615	620
Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met			
625		630	635

Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg Asp Cys
 645 650 655

Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Glu
 660 665 670

Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr Phe Ser
 675 680 685

Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu
 690 695 700

Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu Ile Asp
 705 710 715 720

Thr

<210> 10
<211> 2647
<212> DNA
<213> Rattus norvegicus

<400> 10	
gtcttgtcat caggagacct catttacctt ctaggttaag ggagagaatc tatgaagaga	60
aaggaatagt ctgtgtctcg gtcttgccg ggtcagtgtt tctgagagct cacagtggcc	120
acctgaagca tttttccccca gaatgaatga ctgcctgcc tgagaacaga agagccaaac	180
atgtccccccc acatggccat agggagctgg tttcattttag aagaaaagca aagagagggg	240
aaagctctccc tcatttctcc tccggacggc aaacattcag aaatgacatc acacacccca	300
cagccccggg atgactaagg cagaagtagc ctgagaaaac tctgctctgc cctgagttt	360
agggcacagt tatgcagatg agcgtctggg cgccaggttcc cgcccttcttc ctctgaggaa	420
gtttcttgggt agatcactga cacctcatcc cggcgaggggg gtgaaaactt ggcaccagcc	480
actccccctc cggggcagag caccagaaag agcttggaaag caaggagtcg gcaagcaaac	540
aatgaaggag caagggggca ccgtcagtgg cgccgggagc agccgaggcg gaggagactc	600
ggctatggcc agcctgcagc cgctgcagcc taactacctg tctgtgtgtt tgtttgcaga	660
agaatcatat cagaaaactag caatggagac gctggaggaa ctagactggt gcctagacca	720
gctagagacc atccagacct accgctctgt cagcgagatg gcttcaaaca agttcaaaag	780
gatgctgaac cgggagctga cacacctctc agagatgagc agatcaggga accaagtgtc	840
tgaatacatt tcgaacacgt tcttagacaa gcagaacgat gtggaaatcc catctccac	900
ccagaaggac agggagaaga agaagaagca gcagctcatg acccagataa gtggagtgaa	960
gaaaactgatg cacagctcaa gcctgaacaa cacaagcatc tcacgctttg gagtcaacac	1020
ggaaaatgag gatcatctag ccaaggagct ggaagacctg aacaaatggg gccttaacat	1080

cttcaacgtg gctgggtact cccataatcg gcccctcaca tgcatacatgt acgccatttt
ccagggaaaga gactttctaa agacgtttaa aatctcctcc gacaccttcg taacctacat
gatgacttta gaagaccatt accattctga tgtggcgtat cacaacagcc tgcacgctgc
tgacgtggcc cagtcaacgc acgttctct ctctacgcca gcactggatg ctgtcttcac
agacctggaa atcctggctg ccattttgc agctgccatc catgatgttgc atcatcctgg
agtctccaat cagtttctca tcaatacataaa ttccgaactt gctttgatgt ataatgacga
atctgtgctg gaaaaccatc acctcgctgt gggattcaag ctcccttcaag aggaacatttgc
cgacatctt cagaatctta ccaagaagca acgcccagaca ctcaggaaaa tggtgattga
catggtgtta gcaactgata tgtccaagca catgagcctc ctggctgacc ttaaaacgtat
ggtagaaacc aaaaaggtga cgagctccgg tggatcgatc ctggacaact atactgaccg
gatacagggtt cttegcaaca tggtaacatttgc tgcagacccctt ccaagtcctt
ggagttgtat cggcaatggc ctgatcgatc catggaggag ttttccaaac agggagacaa
agaacgggag agggaaatgg agattagccc aatgtgttat aaacacacag cttctgtgga
aaagtccccag gttggtttca ttgactacat tgtccatcca ttgtgggaga cctggcaga
cctgggttcag cctgatgctc aagacattttt ggacacacta gaagataaca ggaactggta
ccagagtatg attccccaga gcccctctcc accactggac gagaggagca gggactgcca
aggcctttagt gagaagtttc agttcgaact gacccttgaa gaagaggatt ctgaaggacc
ggaaaaggag ggagaaggcc ccaactattt cagcagcaca aagacacttt gtgtgatcga
tccagagaac agggattctc tggaaagagac tgacatagac attgccacag aagacaagtc
tctgatcgac acataatctc ccttgcgttgc gaggtgaaca ttctatcctt gacgagcatg
ccagctgagt ggttagggccc acctaccaga gccaaggcct gcacaaaaca aaggccaccc
ggctttgcag ttacttgagt ttggagccag aatgcaaggc cgtgaagcaa atagcagttc
cgtgctgcct tgccttgccg gcgagcttgg cgagacccgc agctgttagta gaagccagtt
cccagcacag ctaaatggct tgaaaacaga ggacagaaaag ctgagagatt gtcgtcaat
aggtgtttag gggctgtccc gacaggtgac tgaactcact aacaacttca tctataaattc
tcacccatcc tggatcgatc caacccatcc ttgttgcgttgc gcttttttgc taaaatgttt tcgtgttt
gaaatgc

<210> 11
<211> 3133
<212> DNA
<213> *Battus polyvictus*

<400> 11

gaattcgccgc acgagagcac atgctggatg gactctggtt ccgcaccttg tgcagacaaa	60
agtgactggg tggccaggct ttgcttactg tctgagttaa tgaagcttgt ttgataaggt	120
tttctttcaa aaaaaaatta catataaagg atttatcaaa agccctcatg aatatttcat	180
gagttgatac attcggctga atggatttag tgagtcttag tgcgttaactt gcacacaaggc	240
cccatccaca aggaggctgg tgacagagga agcactttgg cgcathttca gaggcaaagg	300
cagcctgata aagctcctgt gacaggctga cttgccatcc tcccagtagtgc ctgctcttgc	360
tctgaagtgc tccaggattg gaaccatcac ggcttccaa attagcctag gacgagtgtg	420
cggacccagc agcctttaa cctgcggcag tgcctttgtt atgttcaaga ctgttgttgt	480
ggatggtgaa agctagcgcg ccacacgaga catgacagca aaaaattctt ccaaagaact	540
tccagcttct gaatctgagg tttgcataaa gactttcaag gagcagatgc gcttggaaact	600
ttagcttcca aagctaccag gaaacagacc tacatctccc aaaatttctc cacgcagttc	660
accaaggaat tcaccatgct tttcagaaa gttgctggtg aataaaagca tccgacagcg	720
gcgtcgcttc actgtggctc atacatgctt tgatgtggaa aatggccctt ctccaggtcg	780
gagcccactg gaccctcaag ccagctcttc ttcaggactg gtacttcatg ccgccttccc	840
tggcacago caacgcagag agtctttctt ctacagatcc gacagcgact atgacttgc	900
accaaaagcg atgtcaagga actcctcact tcccagcgaa caacacggcg atgacctgat	960
tgtcacttct tttgcccagg ttcttgccag cttgcgaatc gtaagaaaca atttcaccct	1020
gctgacaaac cttcacggag caccgaacaa gaggtcgcca gcccgttagtc aggctccagt	1080
caccagagtc agcctgcaag aagaatcata tcagaaacta gcaatggaga cgctggagga	1140
actagactgg tgcctagacc agctagagac catccagacc taccgctctg tcagcgagat	1200
ggcttcaaacc aagtcaaaaa ggatgctgaa ccgggagctg acacacctct cagagatgag	1260
cagatcaggg aaccaagtgt ctgaatacat ttgcacacg ttcttagaca agcagaacga	1320
tgtggaaatc ccatctccca cccagaagga cagggagaag aagaagaagc agcagctcat	1380
gaccctgata agtggagtga agaaactgat gcacagctca agcctgaaca acacaagcat	1440
ctcacgcttt ggagtcaaca cggaaaatga ggatcatcta gccaggagc tggaaagacct	1500
gaacaaatgg ggccttaaca tcttcaacgt ggctgggtac tcccataatc ggcccctcac	1560
atgcatcatg tacgccattt tccaggaaag agaccctcta aagacgttta aaatctcctc	1620
cgacaccttc gtaacctaca tgatgacttt agaagaccat taccattctg atgtggcgta	1680
tcacaacagc ctgcacgctg ctgacgtggc ccagtcacg cacgttctcc tctctacgccc	1740
agcactggat gctgtctca cagacctggaa aatcctggct gccatTTTcagctgcccatt	1800
ccatgtatgtt gatcatctcg gagtctccaa tcagttctc atcaatacaa atccgaact	1860

tgctttgatg tataatgacg aatctgtgct ggaaaaccat cacctcgctg tgggattcaa 1920
gctccttcaa gaggaacatt gcgacatctt tcagaatctt accaagaagc aacgccagac 1980
actcaggaaa atggtgattt acatgggttt agcaactgat atgtccaagc acatgagcct 2040
cctggctgac cttaaaacga tggtagaaac caaaaaggtg acgagctccg gtgttctcct 2100
cctggacaac tatactgacc ggatacaggt tcttcgcaac atggcacatt gtgcagacct 2160
gagcaaccct accaagtccct tggagttgta tcggcaatgg actgatcgca tcattggagga 2220
gtttttccaa cagggagaca aagaacggga gagggaaatg gagattagcc caatgtgtga 2280
taaacacaca gcttctgtgg aaaagtccca ggttggtttc attgactaca ttgtccatcc 2340
attgtggag acctggcag acctgggtca gctgatgct caagacattt tggacacact 2400
agaagataac aggaactggt accagagtat gattccccag agccccccttc caccactgga 2460
cgagaggagc agggactgcc aaggccttat ggagaagttt cagttcgaac tgacccttga 2520
agaagaggat tctgaaggac cgaaaaagga gggagaaggc cccaaactatt tcagcagcac 2580
aaagacactt tgtgtatcg atccagagaa cagggattct ctggaagaga ctgacataga 2640
cattgccaca gaagacaagt ctctgatcga cacataatct ccctctgtgt ggaggtgaac 2700
attctatcct tgacgagcat gccagctgag tggtagggcc cacctaccag agccaaaggcc 2760
tgcacaaaac aaaggccacc tggcttgca gttacttgag ttggagccca gaatgcaagg 2820
ccgtgaagca aatagcagtt ccgtgctgcc ttgccttgcc ggcgagcttg gcgagacccg 2880
cagctgttgtt agaagccagt tcccagcaca gctaaatggc ttgaaaacag aggacagaaa 2940
gctgagagat tgctctgca taggtgttga ggggctgtcc cgacaggtga ctgaactcac 3000
taacaacttc atctataaat ctcacccatc ctgttgcctt ccaacctgtg tgcctttttt 3060
gtaaaaatgtt ttctgtgtt taaaatgcct gttgaatatc tagagtttag tacctccttc 3120
tacaaaacttt ttt 3133

INTERNATIONAL SEARCH REPORT

International application No.

PCT US00/34045

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 9/16, 9/22, 1/20, 15/00, 5/00; C07H 21/04
 US CL. : 435/196, 199, 252.3, 320.1, 325; 536/23.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/196, 199, 252.3, 320.1, 325; 536/23.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MONACO, L. et al. Structure of Two Rat Genes Coding for Closely Related Rolipram-sensitive cAMP Phosphodiesterases. MULTIPLE mRNA VARIANTS ORIGINATE FROM ALTERNATE SPLICING AND MULTIPLE START SITES. J. Biol. Chem. 07 January 1994, Vol. 269, No. 1, pages 347-357, see the entire document, especially Fig. 2 to Fig. 5.	1-18
Y	HUSTON, E. et al. Molecular cloning and transient expression in COS7 cells of a novel human PDE4B cAMP-specific phosphodiesterase, HSPDE4B3. Biochem. J. 1997, Vol. 328, pages 549-558, see the entire document.	1-18

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 MARCH 2001	06 APR 2001
Name and mailing address of the ISA-US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer <i>Dorothy Lawrence Tor</i> TEKCHAND SAIDHA
Faxsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/34045

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

West search, stn search in files medline, capplus, embase, biosis, biotechds and others. Search terms used : human or mammalian phosphodiesterase, and gene or dna or rna or nucleic acid? and others. Issued US patent, EST, genebank and protein data bases search for the claimed SEQ ID NOS.